

REMARKS

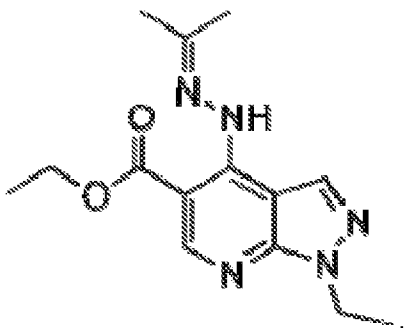
Reconsideration is requested.

Claims 7 and 11 have been additionally canceled, without prejudice, to advance prosecution. Claims 7 and 11-14 are pending. Claims 12-14 will be pending upon entry of the present Amendment.

The Amendment After Final Rejection filed June 22, 2009 has been entered. An RCE is filed herewith to ensure entry of the present Amendment.

Claim 13 has been revised to require monitoring of the patient for improvement in perceptive cognition after the administration of the an etazolate.

Etazolate has the following structure:



The specification describes an example of known methods of monitoring for improvement in perceptive cognition in Example 5, spanning pages 26-27 of the specification. See also, for example, page 6-9 of Dalton (WO 95/11887, of record).

No new matter has been added.

To the extent not made moot by the above amendments, the Section 103 of claims 7 and 11-14 over Ikhlef (U.S. Patent Application Publication No. 2003/0064374) and Dalton (WO 95/11887), is traversed. Reconsideration and withdrawal of the

rejection are requested in view of the following distinguishing comments and the previously submitted evidence.

The rejection is understood to be based on an assertion that treating Alzheimer's disease would necessarily or inherently cause improvements in cognitive deficits, which are a symptom of Alzheimer's disease. The cited art fails to teach or suggest the claimed method, which requires monitoring the treated patient for improvement in perceptive cognition after administration of an effective amount of etazolate.

Rather, the primary reference (Ikhlef) teaches away from this aspect of the presently claimed invention. More specifically, Ikhlef teaches that an advantage of the Ikhlef method is not monitoring the symptoms accompanying the treated neurodegenerative disease. See ¶[0012] of Ikhlef. Ikhlef describes the discovery of a new molecular target (i.e., phosphodiesterase 4B (PDE4B)) for "detecting an excitotoxicity situation or neuronal stress in a subject" (see ¶[0013] of Ikhlef) whereby "the presence of a mutant RNA of phosphodiesterase 4, particularly phosphodiesterase 4B, in a sample from the subject, in particular a form deleted of all or part of the 3' noncoding region" is detected. See ¶[0014] of Ikhlef. Ikhlef further describes as follows:

"The invention also provides for new methods of diagnosis, screening, detection, determination of a predisposition or monitoring the progression or the efficacy of treatment of these diseases." See ¶[0012] of Ikhlef.

"The invention is generally based on the use of a nucleic acid complementary to all or part of the PDE4B gene or messenger, for detecting pathological events related to excitotoxicity, stress, neuronal death, etc." See ¶[0016] of Ikhlef.

Ikhlef teaches away from the claimed method in that Ikhlef describes monitoring treatment with molecular markers relating to the PDE4B gene or messenger.

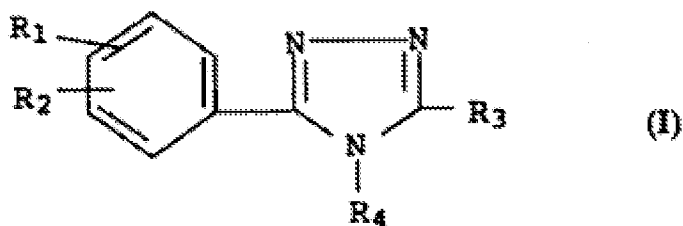
Ikhlef describes that the PDE4B marker was isolated from over 200 separate sequences involving “key players in the excitotoxicity phenomenon” (see ¶[0009] of Ikhlef) in a transgenic mouse model system of a familial form of Amyotrophic Lateral Sclerosis (FALS) involving expression of human superoxide dismutase 1 gene (SOD1) bearing one mutation (G93A). There is no teaching or suggestion in Ikhlef that the Amyotrophic Lateral Sclerosis mutation of the transgenic mouse model of Ikhlef is related to diminished perceptive cognition in patients suffering from Alzheimer’s disease. To the contrary, Ikhlef suggests that the relation between the PDE4B molecular target discovered by Ikhlef for treating ALS, and Alzheimer’s disease is

“based on the goal of reducing the inflammation observed in brain during neurodegenerative processes and not at all on a rationale aiming to directly inhibit neuronal death.” See ¶[0019] of Ikhlef .

Ikhlef therefore fails to suggest monitoring patients after treatment as required by the claimed method and Ikhlef fails to teach or suggest treatment of perceptive cognition, such as by teaching or suggesting a connection or correlation between PDE4B expression and perceptive cognition.

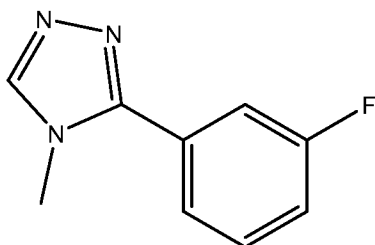
The Examiner’s secondary reference (Dalton), fails to cure the deficiencies of Ikhlef. Rather, Dalton teaches the unpredictability of predicting the function of compounds used for treating Alzheimer’s disease.

More specifically, Dalton describes the use of triazole compounds of the following structure (I) for treatment of Alzheimer’s disease:



Etazolate is not a triazole of the structure of formula (I) of Dalton. Etazolate is not suggested by the triazoles of the structure of formula (I) of Dalton.

Dalton describes the use of the specific compound 3-(3-fluorophenyl)-4-methyl-4H-1,2,4-triazole, having the following structure:



in a model system for treatment learning impairment.

See pages 6-9 of Dalton.

Dalton also describes that the molecular basis for enhancing of memory and cognition of the triazoles of Dalton is related to the enhanced binding and of choline uptake in brain cortex cells treated with the triazoles. See pages 3-4 of Dalton.

There is no teaching or suggestion in Dalton that PDE4B expression is inhibited or effected with administration of the triazoles of Dalton, as is taught by Ikhlef to be of importance in treating ALS with etazolate. There is no teaching or suggestion in Ikhlef that choline uptake is effected by etazolate or other prospective targets of the inhibition of PDE4B expression, as is taught by Dalton to be of importance for treating diminished cognition of patients suffering from Alzheimer's disease. There is no suggestion in the

cited art to have combined the cited art and/or to have made the presently claimed invention even if combined.

Moreover, Dalton describes on pages 3-4 of the reference that compounds having a wide variety of chemical structures have been reported to have “cognition enhancing activity and to be useful for treatment of Alzheimer’s disease.” Many of these compounds however, according to Dalton, also have side effects, such as being antidepressants, which limit their therapeutic potential. Dalton therefore highlights the unpredictability of the functions of chemical structures used to treat diminished cognition in patients suffering from Alzheimer’s disease.

The use of etazolate in the claimed method would not have been obvious in view of the cited combination of art.

For completeness, the applicants note the Examiner’s comment that Dalton was “employed solely for the teaching that Alzheimer’s disease is a memory deficient condition.” See page 2 of the Office Action dated April 20, 2009. The Examiner will appreciate however that a reference must be considered for all that it teaches.

Moreover, the Examiner’s apparent reliance on an alleged inherent teaching in the art can not be a sustainable basis for a *prima facie* case of obviousness. See for example, page 5 of the Office Action dated April 20, 2009 (“It would have been obvious to one of ordinary skill in the art at the time of the invention to have known that by administering etazolate as taught by Ikhlef to treat Alzheimer’s disease, that one would also have been treating the cognitive deficiencies of the disease.”)

The Federal Circuit Court of Appeals has explained the following in In re Rijckaert, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993), for example, with regard to inherency and obviousness:

The mere fact that a certain thing may result from a given set of circumstances is not sufficient [to establish inherency.]” In re Oelrich , 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981) (citations omitted) (emphasis added). “That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.” In re Spormann, 363 F.2d 444, 448, 150 USPQ 449, 452 (CCPA 1966). Such a retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection. See In re Newell, 891 F.2d 899, 901, 13 USPQ2d 1248, 1250 (Fed.Cir. 1989).

Alzheimer’s disease is a progressive neurodegenerative disorder that is characterized by the presence of amyloid deposition and neurofibrillary tangles together with the loss of cortical neurons and synapses (see e.g., Ritchie, K. & Lovestone, S. The dementias. Lancet 360, 1759–1766 (2002); Terry, R.D. et al. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Ann. Neurol. 30, 572–580 (1991)). Abnormalities have also been reported in peripheral tissue supporting the fact that Alzheimer's disease is a systemic disorder (Connolly, G., Fibroblast models of neurological disorders: fluorescence measurement studies TiPS Vol. 19, 171-77 (1998)).

Besides cognitive deficits, Alzheimer’s disease symptoms include, for instance, behavioural disorganization, disability to walk, incontinence, psychiatric complications or metabolic problems. Accordingly, a treatment of Alzheimer’s disease may target any one of the above symptoms, but not necessarily perceptive cognition. In face, as noted

above, Ikhlef apparent suggests a correlation between treatment of inflammation observed in the brain during neurodegeneration associated with Alzheimer's disease and inhibition of PDE4B expression.

As noted in Dalton, a substantial number of drugs presently used for treating Alzheimer's disease are anti-depressants and anti-psychotics, which have no effect on perceptive cognition. Use of these drugs in treatment of Alzheimer's disease would not have suggested the presently claimed invention.

Examples of anti-depressants used in Alzheimer's disease treatment include the following serotonin-reuptake inhibitors: citalopram (Celexa), fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), and trazodone (Desyrel). Suitable anxiolytics include benzodiazepine agonists such as lorazepam (Ativan) and oxazepam (Serax). Antipsychotic medications include dopamine D2 receptors, serotonin 5-HT receptors, alpha-1A-adrenoceptors, histamine H1 receptors: aripiprazole (Abilify), clozapine (Clozaril), haloperidol (Haldol), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), and ziprasidone (Geodon).

The mention in Ikhlef that etazolate can be used to treat inflammation related to Alzheimer's disease would not have suggested the presently claimed invention.

The results presented in the present application are unexpected because, for example, they rely on a previously unknown mechanism of action of etazolate, not previously foreseen or predicted by the cited art, namely the modulation of GABAA receptor causing sAPPalpha production. As described in the application, the applicants have discovered that GABA is involved in cognition and that etazolate, in addition to

being a PDE4 inhibitor, is also a GABAA receptor modulator. These results have been further disclosed by the applicants in Marcade et al (JNC, 106:392-404 (2008)

“Etazolate, a neuroprotective drug linking GABA_A receptor pharmacology to amyloid precursor protein processing”), a copy of which was submitted with the Amendment After Final Rejection of June 22, 2009 and is listed on the concurrently filed PTO 1449 Form.

This publication shows that, by eliciting GABA mechanisms, etazolate further protects against A β peptide and induces the precognitive sAPP α molecule. This dual mode of action of Etazolate is unprecedented.

The remarkable properties of etazolate have led the assignee to initiate clinical trials with this molecule for increasing perceptive cognition in Alzheimer's disease patients. Phase I trials have now been completed and a Phase IIa trial conducted on 197 ambulatory patients suffering from mild to moderate Alzheimer's disease is about to be finalized. As stated in the attached recent Press Release of the company (wherein etazolate is designated EHT0202) (emphasis added):

EHT 0202 has a **novel mechanism** of action when compared to existing Alzheimer's disease therapeutics: it stimulates the α -secretase pathway, thus enhancing the production of the **procognitive** and neuroprotective sAPP α fragment of APP (Amyloid Precursor Protein). ...

Phase I studies demonstrated good tolerability of EHT 0202 in both young and aged healthy volunteers; importantly, no sedation was observed clinically.

Preclinical studies have shown that EHT 0202 protects cortical neurons against A β 42-induced stress and that this neuroprotection is associated with sAPP α induction. EHT 0202 has also **demonstrated pro-cognitive properties in several animal models**: age-related memory impairment and scopolamine-induced amnesia (2). ...

SCHWEIGHOFFER et al.
Appl. No. 10/560,774
Attny. Ref.: 3665-167
Amendment
July 31, 2009

“In light of the neuroprotective and procognitive effects demonstrated by EHT 0202 in preclinical studies, we believe that our drug candidate has the potential to modify the course of Alzheimer’s disease and might open a new era in the treatment of this devastating disease”

The novel mechanism and pro-cognitive effect of etazolate were unexpected and unpredictable from the cited art. The claimed methods would not have been obvious in view of the cited combination of art.

Withdrawal of the Section 103 rejection is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned, preferably by telephone, in the event anything further is required in this regard.

Respectfully submitted,

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